CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
BIS(TRICHLOROMETHYL) SULFONE

Chemical Code # 001865, Tolerance # 50426
SB 950 # 530
Original date: September 24, 2002

I. DATA GAP STATUS

Chronic toxicity, rat:	Data Gap, no study on file.
Combined, rat:	Data Gap, no study on file.
Chronic toxicity, rat:	Data Gap, no study on file.
Chronic toxicity, dog:	Data Gap, no study on file.
Oncogenicity, rat:	Data Gap, no study on file.
Oncogenicity, mouse:	Data gap, no study on file
Reproduction, rat:	Data gap, no study on file.
Teratology, rat:	No data Gap, no adverse effects
Teratology, rabbit:	Data Gap, no study on file.
Gene mutation:	Data gap, inadequate studies, Possible adverse effect indicated.
Chromosome effects:	Data gap, inadequate study, adverse effect indicated.
DNA damage:	Data gap, inadequate study, no adverse effect indicated
Neurotoxicity:	Data gap, inadequate study, adverse effect indicated

---

Toxicology one-liners are attached.

All record numbers through 114691 examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T020924
Original: J. Kishiyama and J. Gee, September 24, 2002

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC TOXICITY, RAT

No study on file.

CHRONIC TOXICITY, DOG

No study on file.

ONCOGENICITY, RAT

No study on file.

ONCOGENICITY, MOUSE

No study on file.

REPRODUCTION, RAT

No study on file.

TERATOLOGY, RAT

** 50426 - 015 114689 Nemec, M. D., Study Director. " A Teratology Study in Rats with N-1386 Biocide Technical." (WIL Research Laboratories, Inc., Laboratory Project ID WIL-27038, March 20, 1987.) N-1386 Technical (lot 928, 97%) was administered by gavage at doses of 0 (Mazola ® corn oil), 2, 10, or 50 mg/kg/day to 25 bred female rats/group during gestation days 6 through 15. There was an increase in the incidence of soft stools, matted anogenital and urogenital areas, hair loss, lower body weight (7 to 10%) and reduced food consumption (25 to 47%) at 50 mg/kg/day . Food consumption was also reduced 10 to 24% and there was body weight loss days 6 - 9 of dosing for the mid dose group. Maternal NOEL = 2 mg/kg/day (body weight, food consumption, clinical signs). Fetal weight was reduced by 5.7% at 50 mg/kg/day. The mean incidence of early resorptions was increased for the high dose group, being 1.3 versus 0.9 for control with one dam having 9/15 early resorptions, influencing the mean incidence. This difference was not statistically significant but was stated to exceed the historical control range. Developmental NOEL = 10 mg/kg/day. The incidence of 14th rudimentary ribs was increased for high dose litters. There were no treatment-related malformations. ACCEPTABLE with no adverse effects. (Kishiyama and Gee, 9/19/02).

TERATOLOGY, RABBIT

No study on file.

GENE MUTATION

50426 - 013 114684 Majeska, J. B., Study Director. "Mutagenicity Evaluation in *Salmonella Typhimurium*." (Stauffer Chemical Co., Report No. T-10042, October 14,1980.) N-1386 (purity not stated) was tested at ten concentrations ranging from 0.156 to 33.33 :g/plate without metabolic activation and at 0.4, 1.2, 3.7, 11.1 and 33.3 :g/plate with metabolic activation (rat liver S9 Mix) for mutagenic potential using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 by plate incorporation. There were triplicate plates per concentration and two trials. An increase in the average number of revertants was repeated with N-1386 treatment without activation with *Salmonella* strains TA1535 and TA 100 and with S9 Mix for strain TA 1535. Other strains were negative. UNACCEPTABLE. Ungradable (test article purity and stability; individual plate data). (Kishiyama and Gee, 9/18/02).

011 045387 Same study (without protocol and SOP) as 013 114684.

50426 - 013 114686 Matheson, D. W. "Mutagenicity Evaluation of N-1386 in the Mouse Lymphoma Forward Mutation Assay." (Litton Bionetics, Inc., LBI Project No. 20839, March 1978.) N-1386 (purity not stated) was evaluated for potential mutagenicity using mouse lymphoma L5178Y cells at concentrations ranging from 0.5 to 1.0 : g/ml without S9 Mix and 0.5 to 4 : g/ml with mouse liver S9 Mix in the first trial and from 0.75 to 2.0 : g/ml without S9 Mix in a second trial. There was a single culture per concentration. Exposure was for 4 hours followed by a three-day expression period. Exposed cells were plated for mutant expression with BrdU (number of plates was not reported). An increase in mutation frequency was observed in the first test at the highest concentration with a relative growth of 0.9%. This was not observed in the repeat test. There was no second trial with activation. UNACCEPTABLE (test article purity not stated, no repeat trial with activation, number of plates for mutant selection not stated, single culture per concentration). Not upgradable. (Kishiyama and Gee, 9/18/02).

011 045388 Same study (without protocol) as 013 114686.

50426 - 014 114687 Majeska, J. B. "Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test." (Stauffer Chemical Company, Report No. T-10138, December 15, 1980.) N-1386 (purity not stated) was evaluated at concentrations ranging from 0.0125 to 3.0 : g/ml with and without metabolic rat liver activation (S9 Mix) with L5178Y $TK^{+/-}$ Mouse Lymphoma cells for mutagenic and genotoxic (chromosomal aberrations and sister chromatid exchange) potential. For all three endpoints, cells were exposed at one time for 4 hours, then subdivided. For mutation frequency, cells were grown for three days for expression followed by plating in selection medium for resistance to trifluorothymidine (triplicate plates per initial culture?). After 9 - 11 days, plates were scored for mutant colonies. For cytogenetics, cells were resuspended in medium containing BrdU and grown for 21 hours in suspension. Colcemid was added for an additional three hours. Cells were harvested, fixed, spread on slides and stained as appropriate. For aberrations, 50 metaphases were scored and a mitotic index recorded. For sister chromatid exchanges, 15 - 20 cells per concentration were scored. Results: N-1386 at the two highest concentrations (0.1 and 0.2 : g/ml without activation) an increased mutant frequency was found the first trial but this result was not repeated in a second trial. In the cytogenetic assays, there were no significant increases in either aberrations or SCE's. UNACCEPTABLE (Mutation Assay may be upgradeable with purity and stability of test article. Cytogenetic assays were based on the evaluation of one culture per experimental point with a minimal number of cells scored. (Kishiyama and Gee, 9/18/02).

011 045389. Same study but not as complete as 014 114687.

50426 - 011 045385 Brusick, D. J., Director. "Mutagenicity Evaluation of Sample #300." (Litton Bionetics, Inc., LBI Project No. 2683, October 26, 1976.) Sample # 300 was tested at concentrations of 0, 0.1, 1, 10, 100 and 500 : g/plate with and without rat liver metabolic activation for potential mutagenic activity using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 and *Saccharomyces cerevisiae* D4. There was a single replicate per concentration. There was a limited second trial with TA1535 at 1 and 10 : g/plate to confirm the suggested result in trial 1. There was an increase in the number of revertants in *Salmonella* strain TA1535, especially with activation, but also without S9. Concentrations of 100 and 500 : g/plate were toxic to all strains, including *Saccharomyces*. Positive controls were functional. UNACCEPTABLE (test article purity not given, single plate per concentration). Not upgradeable.

50426 - 011 045385 Brusick, D. "Mutagenicity Evaluation of Sample #400." (Litton Bionetics, Inc., LBI Project No. 2683, October 26, 1976.) Sample #400 was tested at concentrations of 0, 0.1, 1, 10, and 100 : g/plate with and without metabolic activation for

potential mutagenic activity using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 and *Saccharomyces cerevisiae* D4. There was a single plate per concentration in a single trial. The number of revertants was increased in *Salmonella* strain TA1535 with and without activation. UNACCEPTABLE (no test article purity, single plate per treatment). Not upgradeable. (Kishiyama and Gee, 9/23/02).

CHROMOSOME EFFECTS

50426 - 013 114680 Stetka, D. "Mutagenicity Evaluation of N-1386 in the Sister Chromatid Exchange Assay in L5178Y Mouse Lymphoma Cells." (Litton Bionetics, Inc., LBI Project No: 20990, January 1979.) N-1386, with and without metabolic activation (S9 Mix), was tested at concentrations of 0 (DMSO), 0.313, 0.625, 1.25, 2.5, and 5.0 (+S9 only) : g/ml for potential genotoxicity using mouse lymphoma cells. Cells were exposed for 4 hours followed by continued incubation for 20 hours in the presence of BrdU. There were 20 cells scored per single culture per concentration. SCE's/cell were significantly increased with N-1386 treatment at 0.313, 0.625, 1.25 and 2.5 : g/ml without metabolic activation (S9) and at 2.50 : g/ml with S9 Mix**.** UNACCEPTABLE (limited description of the test methods, no description of test article for purity). Possibly upgradeable. (Kishiyama and Gee, 9/17/02)

011 45390. Exact duplicate of 013 114680.

50426 - 014 114687 Majeska, J. B. "Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test." (Stauffer Chemical Company, Report No. T-10138, December 15, 1980.) N-1386 (purity not stated) was evaluated at concentrations ranging from 0.0125 to 3.0 : g/ml with and without metabolic rat liver activation (S9 Mix) with L5178Y $TK^{+/-}$ Mouse Lymphoma cells for mutagenic and genotoxic (chromosomal aberrations and sister chromatid exchange) potential. For all three endpoints, cells were exposed at one time for 4 hours, then subdivided. For mutation frequency, cells were grown for three days for expression followed by plating in selection medium for resistance to trifluorothymidine (triplicate plates per initial culture?). After 9 - 11 days, plates were scored for mutant colonies. For cytogenetics, cells were resuspended in medium containing BrdU and grown for 21 hours in suspension. Colcemid was added for an additional three hours. Cells were harvested, fixed, spread on slides and stained as appropriate. For aberrations, 50 metaphases were scored and a mitotic index recorded. For sister chromatid exchanges, 15 - 20 cells per concentration were scored. Results: N-1386 at the two highest concentrations (0.1 and 0.2 : g/ml without activation) an increased mutant frequency was found the first trial but this result was not repeated in a second trial. In the cytogenetic assays, there were no significant increases in either aberrations or SCE's. UNACCEPTABLE (Mutation Assay may be upgradeable with purity and stability of test article. Cytogenetic assays were based on the evaluation of one culture per experimental point with a minimal number of cells scored. (Kishiyama and Gee, 9/18/02).

DNA DAMAGE

50426 - 013 114682 Majeska, J. B., Study Director. " N-1386: Morphological transformation of BALB/3T3 Cells." (Stauffer Chemical Company, Report No. T-10139, December 5, 1980.) N-1386 (purity not stated) was assayed at concentrations ranging from 0.005 to 0.08 : g/ml for its potential to transform BALB/3T3 cells in culture. A preliminary toxicity test was conducted to select the concentrations for the primary study using triplicate plates and colony formation. In the primary study, 15 flasks were used for each concentration to evaluate formation of transformed foci. Cells were exposed for 3 days to the test article, followed by several weeks of incubation to allow foci growth. No activation was included, without justification. There was no evidence of increased morphological transformation of

BALB/3T3 cells with N-1386 treatment. The positive control, 3-methylcholanthrene, was functional. UNACCEPTABLE, not ungradable (no test article purity and stability, no activation included without justification). (Kishiyama and Gee, 9/18/02).

011 045391. Same study (without S.O.P.) as 13 114682.

NEUROTOXICITY

50426 - 011 045384 Sprague, G. L., Study Director. "Neurotoxicity Evaluation of N-1386 Technical: Effect on Rat Cholinesterases (T-10599)." (Stauffer Chemical Company, Richmond Laboratory, Toxicology report: T-10599, May 20, 1982.) N-1386 (lot 216, purity not stated) at a dose of 500 mg/kg was administered via a single oral gavage to male adult Sprague-Dawley rats (number not stated). *In vivo* plasma and brain cholinesterase activity were measured 2, 4 and 24 hours after dosing. There was no significant inhibition of either cholinesterase compared with untreated controls. *In vitro* effects were measured at 0, 5, 10 and 50 :M added directly to rat plasma. There was almost complete inhibition at 50 :M. N-1386 was added to brain homogenates at 0, 1, 5 or 10 :M. There was a concentration dependent inhibition at 5 and 10 :M. The effect of anti-cholinergic drugs (atropine and scopolamine) on mortality when administered just prior to N-1386 treatment (505, 600, 713, 848 or 1008 mg/kg) to 10 male rats/group was studied. Neither compound significantly increased the LD-50 or the time to death. Atropine did, however, reduce the incidence of diarrhea and scopolamine reduced the incidence of both diarrhea and behavioral depression. The conclusion was that N-1386 inhibits cholinesterase but was not responsible directly for the lethality. Supplemental data. (Kishiyama and Gee, 9/20/02).

OTHERS

50426 - 016 114691 Sauerhoff, M. W., and Karen M. MacKenzie. "21-Day Dermal Toxicity Study in Rabbits with N-1386 Technical Biocide." (Hazleton Laboratories America, Inc., Laboratory Project ID HLA No. 6142-102, January 7, 1987.) N-1386 Technical (lot 928, 97%) was administered dermally for 5 days/week for 3 weeks, 6 hour exposure/day, at doses of 0 (mineral oil), 0.8, 2.0 or 5.0 mg/kg to 5 New Zealand White rabbits/sex/group. Two deaths (one low dose and one high dose male) were considered unrelated to the test article. Increased incidences of dermal irritation (edema, erythema, desquamation and fissuring) occurred in the high dosage group (5 mg/kg) in the treated area. On a few occasions, animals in the mid-dose group were scored as having "slight" findings. Microscopic changes were limited to the high dose animals with hyperkeratosis and mononuclear cell infiltration in a few animals. No other treatment related effects were reported. Dermal NOEL = 2 mg/kg (histological changes). Systemic NOEL $\geq$ 5 mg/kg (no effects). UNACCEPTABLE. Upgradeable (Dosing material analysis to confirm homogeneity and test article content). (Kishiyama and Gee, 9/19/02).